Remarks

Claims 1-19 have been amended.

The amendment to claims 1, 7, 12, 14 and 17 that indicates that the recited composition is such that the Agent component present in a quantity of the composition having 250 mg of the Agent will substantially completely dissolve within 60 minutes in 500 ml of an aqueous medium at a temperature of 37 °C and having a pH of about 1.5 finds support in Applicants' specification, *inter alia*, at paragraphs [0172], [0235] and Table 1 of the published application.

Amendments that are formalistic in nature have been made to claims 2-6, 8-11, 13, 15, 16, 18 and 19.

Claim 7 has been rewritten in independent format.

No new matter has been added by any of the amendments.

1. **Priority Documents**

The Examiner asserts that no support can be found in Applicants' priority documents 0204392.5 and 0212462.6 for the currently claimed subject matter in the subject application.

Applicants do not acquiesce to the Examiner's assertion. However, since this matter does not impact the rejections currently of record, Applicants will not address the Examiner's comments in the subject response, but reserve the right to do so in a future submission.

2. **Information Disclosure Statement**

Applicants have submitted an IDS to make of record the circumstances regarding the controlled, confidential and non-commercial testing of a pharmaceutical composition falling within the scope of one or more of the present claims, which tests were carried out at least in part in the United States more than one year before the filing date of the present application as a part of clinical trials for the collection of data for presentation to the FDA during the regulatory review period preceding the approval of the drug Iressa (gefitinib tablets). It is Applicants' belief that the circumstances of this clinical testing are such that it does not constitute a "public use" or any other prior art event under 35 U.S.C. § 102. However, what are believed to be the relevant circumstances are presented in the IDS for completeness of the record and evaluation by the

Examiner. Applicants respectfully request that in the next communication the Examiner provide written confirmation of consideration of the content of the IDS.

3. **Rejections under 35 U.S.C. 103(a)**

A. the '934 patent in view of WO '984

Claims 1, 2, 4-6, 8-11, 13, 16, 17 and 19 are rejected as allegedly obvious over U.S. Patent No. 4,344,934 to Martin *et al.* ("the '934 patent") in view of published PCT application WO 98/38984 to Shenoy *et al.* ("WO '984"). The Examiner asserts that the '934 patent teaches the combination of a poorly soluble compound with a pharmaceutically acceptable water-soluble polymer and a wetting agent. More specifically, the Examiner asserts that Martin teaches that drugs that "give incomplete and irregular absorption when taken orally" are good candidates for combination with water-soluble polymers such as hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) to increase the drug's bioavailability. The '934 patent is acknowledged as not disclosing quinazolines, such as Iressa, as exemplary of a poorly soluble class of drugs and thus, the Examiner relies on WO '984 for the teaching that certain quinazoline derivatives have poor aqueous solubility and hence low bioavailability. According to the Examiner, a person of ordinary skill in the art would have been motivated to add wetting agents and polymers such as HPMC and HPC to a composition of Iressa "in order to increase solubility and improve the bioavailability of the quinazoline drug."

Applicants respectfully disagree with the Examiner's rejection of these claims as allegedly obvious over the '934 patent in view of WO '984 for at least the following reasons.

First, the '934 patent is directed toward increasing the rate of dissolution of poorly soluble compounds such as griseofulvin to enhance their bioavailability through the addition of a water-soluble polymer and a wetting agent. The solubility of griseofulvin is pH insensitive due to its lack of acidic or basic functionalities capable of forming salts. Other suitable poorly soluble compounds described in the specification of the '934 patent include steroids such as medrogestone, progesterone and estradiol and rigid tricyclic compounds such as 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carboxamide and 5H-dibenzo[a,d]cycloheptene-5-carboxamide (see, *e.g.*, col. 4, lines 15-18). Just like griseofulvin, all of these compounds would also be

understood to be pH insensitive in that increasing or decreasing the pH of the media in which these compounds are present would not significantly alter their solubility. In fact, the '934 patent does not teach or suggest the combination of any compounds other than pH insensitive compounds with water-soluble polymers and wetting agents.

In contrast, Iressa by itself (*i.e.*, in the absence of any additional components) is pH sensitive as reflected by the fact that it is highly soluble in the acidic environment of the recipient's stomach (see, *e.g.*, the results of Table 1 in Applicants' specification). In light of its high solubility, Iressa would not have been considered for use in the compositions described in the '934 patent.

The Examiner cites WO '984 for teaching quinazolines as poorly soluble compounds and asserts that it would have been obvious to combine them with the water soluble polymers of the '984 patent. Applicants submit that WO '984 teaches formulations of quinazolines that require excipients such as polyglycolized lipids (*e.g.,* monoglycerides, diglycerides or triglycerides) (see page 39, lines 1-10) in the presence of polyethylene glycol (PEG) derivatives (see page 49, lines 8-20) as a means for improving bioavailability. Such disclosure actually teaches away from the expectation of success of a person of ordinary skill in the art in using only the non-glyceride polymers described in the '934 patent in combination with an anionic or cationic wetting agent as a means to enhance the bioavailability of quinazolines.

Applicants believe that a portion of the Iressa administered to a mammalian recipient would precipitate out of solution as it passes from the recipient's stomach to the higher pH environment of the mammal's upper GI tract (*e.g.*, the small intestine) (see, *e.g.*, paragraph [0008] of Applicants' published application). It was discovered that water-soluble cellulose ethers or esters of water-soluble cellulose ethers helped to maintain the Iressa as a solution as it made this transition. Thus, Applicants' inclusion of a water-soluble cellulose ether or an ester of a water-soluble cellulose ether in the claimed pharmaceutical composition of Iressa is not for the purpose of dissolving an otherwise poorly soluble solid drug to increase its bioavailability but rather for the purpose of maintaining Iressa, which is highly soluble upon oral adminstration, as a solution at the higher pH of the upper GI tract. There is no teaching or suggestion in the '934 patent or WO '984 of this use of the described water soluble glyceride or non-glyceride polymers

because the focus of the '934 patent and WO '984 disclosures is how to increase the solubilities of poorly soluble compounds. Accordingly, a person of ordinary skill in the art would not have considered Iressa as a candidate for combination with the solubilizing excipients described in the '934 patent and WO '984.

Second, in describing suitable water-soluble polymers, the '934 patent does not differentiate between water-soluble cellulose ethers and other water-soluble polymers such as polyvinylpyrrolidone, block copolymers of ethylene oxide and propylene oxide, and polyethylene glycol. Because the focus of the '934 patent is the use of various water-soluble polymers to solubilize poorly soluble compounds so as to increase their bioavailability, any of the aforementioned polymers are indicated as being effective. However, Applicants independently discovered that water-soluble polymers such as polyvinylpyrrolidone, block copolymers of ethylene oxide and propylene oxide, and polyethylene glycol are not suitable for maintaining the solubility of Iressa as it enters the upper GI tract of a recipient to whom Iressa is administered. Accordingly, even if a person of ordinary skill in the art were to consider the '934 patent, there is no teaching or suggestion that certain of the described water-soluble polymers (such as the methyl cellulose, HPMC and HPC) would prove to be effective for Applicants' intended purpose of maintaining the solubility of Iressa while other described water-soluble polymers would not be effective. WO '984 cannot remedy this deficiency present in the '934 patent. For this reason, the '934 patent, either alone or in combination with WO '984 cannot render Applicants' claimed subject matter obvious. Applicants request that this rejection be withdrawn.

Applicants would like to bring to the Examiner's attention that composition claim 7, which the Examiner did not reject as obvious over the combination of the '934 patent in view of WO '984, has been rewritten in independent form.

Applicants would also like to bring to the Examiner's attention that method claim 18, which the Examiner also did not reject as obvious over the combination of the '934 patent in view of WO '984, is directed to a method for inhibiting the rate of precipitation of the Agent from solution in the GI tract of a patient in need of the Agent comprising orally administering to said patient a composition that comprises the Agent and a water-soluble cellulose ether or an

ester of a water-soluble cellulose ether. This method is not addressed in any of the cited art. The sole ground for rejection of claim 18 was, as discussed below, based on U.S. Patent No. 6,287,599 which relates to sustained release formulations. Claims 1, 7 and 12, from which claim 18 depends, have been amended to clarify that the recited composition is not a sustained release formulation.

B. the '934 patent and WO '984 further in view of the '599 patent

Claims 1-14 and 16-18 are rejected as allegedly obvious over the '934 patent and WO '984 as applied to claims 1, 2, 4-6, 8-11, 13, 16, 17 and 19 and further in view of U.S. Patent No. 6,287,599 to Burnside *et al.* ("the '599 patent"). The Examiner relies on the '599 patent for its alleged teaching of sustained release agents (*e.g.*, HPMC), enteric agents (*e.g.*, HPMC phthalate), bulking agents, disintegrating agents, antiadherents, glidants, lubricants and binding agents and asserts that these excipients are described in amounts that are within the ranges recited in Applicants' claims, specifically citing claim 12.

Applicants respectfully disagree with the Examiner's rejection of these claims as allegedly obvious over the '934 patent and WO '984 and further in view of the '599 patent for at least the following reasons.

First, as discussed in section A above, neither the primary reference (the '934 patent) nor the secondary reference (WO '984) would have been considered by one of ordinary skill in the art to be pertinent to Applicants' claimed subject matter. The '599 patent cannot remedy this defect present in the '934 patent and WO '984. Therefore, the combination of the '934 patent and WO '984 and the '599 patent would not render Applicants' claims obvious.

Second, the '599 patent is directed to sustained release formulations of pharmaceutically active compounds. This is apparent from the title of the '599 patent, Tables 2 and 4 which depict compound dissolution over a period of time, and the requirement that the formulation contain at least one non-pH-dependent sustained release agent (see *e.g.*, column 1, lines 32-38 and 58-67). Thus, it is the purpose of sustained release agents such as HPMC to slow or limit the rate at which the drug of interest goes into solution. In contrast, Applicants' claimed composition is not a sustained release formulation and the claims have been amended to more clearly indicate this

fact (*i.e.*, that the Iressa or a pharmaceutically acceptable salt thereof ("the Agent") that is present in the claimed composition will be substantially completely dissolved within about 60 minutes in an aqueous medium at a temperature of 37° C and having a pH of about 1.5). As submitted by Applicants in section A above, the purpose of the recited water soluble cellulose ethers and the esters of water soluble cellulose ethers in Applicants' claimed formulation is to maintain the solubility of the Iressa that is present in the composition and that is readily dissolved in the acidic environment of the stomach of the recipient to whom the Iressa is administered. Because the Iressa is already substantially completely in solution in the low pH environment of the stomach following oral administration, there is no sustained release aspect associated with the claimed formulation. Therefore, the '599 patent, either alone or in combination with the '934 patent and/or WO '984 does not render Applicants' claims obvious. Applicants request that this rejection be withdrawn.

C. the '934 patent and WO '984 and the '599 patent further in view of the '536 patent

Claims 1-19 are rejected as allegedly obvious over the '934 patent and WO '984 and the '599 patent as applied to claims 1-14 and 16-18 and further in view of U.S. Patent No. 5,641,536 to Lech *et al.* ("the '536 patent"). The Examiner relies on the '536 patent for its alleged teaching of a tablet coating method that discloses a tablet film coating that comprises all of the excipients recited in Applicants' claim 15.

Applicants respectfully disagree with the Examiner's rejection of these claims as allegedly obvious over the '934 patent and WO '984 and the '599 patent and further in view of the '536 patent for at least the following reason.

As discussed in sections A and B above, neither the primary reference (the '934 patent) nor the secondary references (WO '984 and the '599 patent) would have been considered by one of ordinary skill in the art to be pertinent to Applicants' claimed subject matter. The '536 patent cannot remedy these defects present in the '934 and '599 patents and WO '984 because the '536 patent simply describes a traditional film coating method and does not teach or suggest Applicants' claimed subject matter. Therefore, the '536 patent, either alone or in combination

with the '934 patent, WO '984 and/or the '599 patent does not render Applicants' claims obvious. Applicants request that this rejection be withdrawn.

4. Conclusion

The foregoing amendments and remarks are being made to place the application in a condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which my be required, including any required extension of time fees, or
to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

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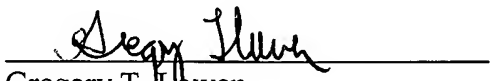
Respectfully submitted
Morgan, Lewis & Bockius LLP

Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: 202-739-3000
Fax: 202-739-3001



Gregory T. Lowen
Registration No. 46,882
Direct: 202-739-5915